REMARKS

Claims 1-16 are pending in the present application. Claims 1, 4, 7, 9, 10, and 12 have been amended and claims 5 and 6 has been cancelled without prejudice to or disclaimer of the subject matter contained therein. New claim 17 has been added. Support for the new and amended claims can be found throughout the specification and claims as originally filed, for example on page 16, lines 21-23 (original claim 6). No new matter enters by way of this amendment. Upon entry of the foregoing amendment, claims 1-4 and 7-17 will be pending.

Reexamination of the application and reconsideration of the rejections and objections are respectfully requested in view of the above amendments and the following remarks, which follow the order set forth in the Office Action.

I. Introductory Comments

Prior to addressing the rejections of record, a brief description of the disclosure is provided for the convenience of the Examiner. The disclosure provides a wound dressing comprising a therapeutic agent and a matrix comprising polymers joined by cross-linkages which cross-linkages comprise oligopeptidic sequences which are cleavable by a kallikrein such that the rate of release of the therapeutic agent increases in the presence of the kallikrein, where the oligopeptidic sequence comprises -Phe-Arg-Ser-Ser-Arg-Gln- or Met-Ile-Ser-Leu-Met-Lys-Arg-Pro-Gln-. The therapeutic agent is contained within or beside a matrix of polymers crosslinked to each other by oligopeptide sequences. As the present specification discusses, "[t]he principle underlying the present invention is that the cross-linked polymers would behave as both an enzyme sensor and as an [sic] pain-dependent delivery system." Specification at page 3, lines 27-29. The specification discloses that in "the absence of elevated levels of kallikreins the oligopeptidic sequences remain intact, keeping pore size small and preventing (or at least keeping to low levels) the release of the therapeutic agent. Elevated pain protease (e.g. in wound infection or wound chronicity) hydrolyse the oligopeptidic sequences which results in increased pore size and permeability." *Id.* at lines 29-33.

II. Election of Species

Applicants affirm the election of the sequence Phe-Arg-Ser-Ser-Arg-Gln and a pain relieving agent, in claims 6 and 7, respectively, as elected during the telephone conference on

November 3, 2006. Applicants acknowledge the finality of the election of species requirement, but maintain their traversal as the Patent Office has not proven that the search and examination of the entire application would impose an undue burden. Applicants submit that the complete examination would be handled most expeditiously by treating all of the pending claims as a single entity. As MPEP 803 directs, "[i]f the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions." Applicants respectfully submit that the Examiner has not shown that a search and examination of the entire application would cause a serious burden. Rather, a serious burden would arise if the application were restricted.

III. Objections to the Specification

The Examiner has objected to the disclosure because the "contents of the Specification should be clearly divided into Background, Summary, and Descriptions." *Office Action* at page 3. In view of the amendments to the specification, the objections are moot, and Applicants respectfully request reconsideration and withdrawal of the objections to the specification.

IV. Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1, 9, and 11-15 have been rejected for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter. *Office Action* at pages 3-4. Claim 1 has been rejected as allegedly it "is unclear how the [recited] matrix is formed" and it is not clear "what is making the cross-linkage." *Office Action* at pages 3-4.

Applicants respectfully submit that the skilled artisan would understand the term matrix when viewed in the context of the claims and the specification. For example, the claim recites that the matrix comprises polymers joined by cross-linkages, which cross-linkages comprise oligopeptidic sequences which are cleavable by a kallikrein. The skilled artisan would understand that the matrix is formed by polymers cross-linked by oligopeptidic sequences. Furthermore, it would also be understood that the oligopeptidic sequences form the cross-linkage between the polymers. Such a reading is further supported by the specification, for example, on page 5, beginning on line 29, which discloses that the polymers are joined by cross-linkages which comprise cleavable oligopeptidic sequences. As such, Applicants respectfully submit that the term is clear when read in light of the specification.

The Examiner has rejected claims 11-15 due to the recitation of "barrier layer" as it is allegedly "unclear from the Specification and the claims what this barrier layer is and how this is different from the cross-linker polymer matrix." *Office Action* at page 4. Again, the skilled artisan would readily understand the term in light of the claim and the specification. *See, e.g. Specification* at page 9, line 27 through page 12, line 13. Based on such disclosure, the skilled artisan would readily understand the term "barrier layer."

Claim 12 has been rejected as the phrase "occlusive fashion" is allegedly unclear. *Office Action* at page 4. Again, the skilled artisan would understand the term based on a reading of the claims in view of the specification. For example, the specification discusses barrier layer compositions having an apertured sheet. *Specification* at page 10, lines 27-30. The specification further discusses that typically the apertured sheet is blocked by the barrier material. *Specification* at page 11, lines 11-13. The skilled artisan would understand the term "occlusive fashion" when read in the context of the claims and the specification. As such, Applicants respectfully submit that the term is clear when read in light of the specification and knowledge of one skilled in the art.

Claim 1 has further been rejected as allegedly there is insufficient antecedent basis for" the limitation "the protease." *Office Action* at page 4. Claim 1 has been amended to recite "kallikrein" rather than "protease." In view of such amendment, Applicants submit that this rejection is moot.

Claim 9 has been rejected as the recitation of "the wound contacting layer" allegedly lacks sufficient antecedent basis. *Id.* Claim 9 has been amended. In view of this amendment, the rejection of claim 9 under 35 U.S.C. § 112, second paragraph is moot.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1, 9, and 11-15 under 35 U.S.C. § 112, second paragraph.

V. Claim Rejections under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 1-5 and 7-16 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

According to the Office Action, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. The Examiner apparently bases the rejection on the recitation of "a matrix comprising polymers joined by cross-linkages that comprise oligopeptidic sequences."

The purpose of the written description requirement is to ensure that the inventors had possession of the claimed subject matter, *i.e.*, to ensure that the inventors actually invented what is claimed. *Gentry Gallery Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479, 45 USPQ2d 1498, 1503 (Fed. Cir. 1998); *Lockwood v. American Airlines*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Alton*, 76 F.3d 1168, 1172, 37 USPQ2d 1578, 1581 (Fed. Cir. 1996). A specification need not describe that which is well known. *Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005). If a person of ordinary skill in the art would, after reading the specification, understand that the inventors had possession of the claimed invention, even if not every nuance, then the written description requirement has been met. *In re Alton*, 76 F.3d at 1175, 37 USPQ2d at 1584. A person of ordinary skill in the art would, after reading the present specification, understand that the Applicants had possession of wound dressings comprising a therapeutic agent and a matrix comprising polymers joined by cross-linkages, which cross-linkages comprise oligopeptidic sequence cleavable by a kallikrein, where the oligopeptidic sequences comprise, for example, the sequence –Phe-Arg-Ser-Ser-Arg-Gln-, and therefore, the claimed invention.

The specification describes a matrix comprising polymers joined by cross-linkages which cross-linkages comprise oligopeptidic sequences that include the sequence Phe-Arg-Ser-Ser-Arg-Gln or Met-Ile-Ser-Leu-Met-Lys-Arg-Pro-Gln-, which are cleavable by a kallikrein. The specification describes numerous polymers for use in the matrix, such as non-ionic surfactants, polyalkoylated alcohols, alkyl or dialkyl polyglycerol compounds, polyethyloxylated alcohols, polymers of acrylamide, polynucleotides, polypeptides, and carbohydrates. *See, e.g. Specification*, at page 5, lines 4-8. In addition, the specification provides examples of synthetic and natural polymers that find use in the matrix as recited in the claims. *See, e.g. Specification*, at page 5, lines 10-22. The specification further discloses that the polymers can be homopolymers or copolymers. *Specification* at page 4, lines 16-17. In addition, the specification teaches cleavable peptidic sequences for use in cross-linking the polymers to form the matrix. *Specification* at page 5, line 29 through page 6, line 2. The specification further describes oligopeptidic sequences that can be cleaved by kallikreins and provides sequences which are degraded by such proteases. *Specification*, at page 7, lines 25-28. In addition, the specification describes numerous examples of therapeutic agents that can be used in the preparation of matrices for use in the wound dressings of the present invention.

Specification, at page 8, line 8 through page 9, line 9. Based on such disclosure, the specification describes matrices comprising polymers joined by cross-linkages that comprise oligopeptidic sequences.

In sum, because the specification demonstrates that Applicants had possession of the claimed wound dressings, and have provided an adequate description of the recited matrix, the specification satisfies the written description requirement of 35 U.S.C § 112, first paragraph, and the rejection of claims 1-5 and 7-16 should be withdrawn. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

VI. Claim Rejections under 35 U.S.C. § 102(e)

Claims 1-16 have been provisionally rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by copending U.S. Application Publication No. 2005/0159695 (hereinafter "Cullen *et al.*), which, as the Examiner notes, has a common inventor with the present application. *Office Action* at page 9. Applicants respectfully traverse for at least the following reasons.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The examiner has not shown that Cullen *et al.* discloses all of the features of claim 1, for example, oligopeptidic sequences comprising -Phe-Arg-Ser-Ser-Arg-Gln- or Met-Ile-Ser-Leu-Met-Lys-Arg-Pro-Gln-.

Claim 1 is directed to a wound dressing comprising a therapeutic agent and a matrix comprising polymers joined by cross-linkages which cross-linkages comprise oligopeptidic sequences which are cleavable by a kallikrein such that the rate of release of the therapeutic agent increases in the presence of the kallikrein, where the oligopeptidic sequence comprises the elected sequence of -Phe-Arg-Ser-Ser-Arg-Gln-. The Examiner has not shown that the cited reference discloses all of the features of the currently claimed invention. For example, the Examiner has not pointed to any disclosure in Cullen *et al.* that discloses the recited sequence, or even any oligopeptidic sequence.

Accordingly, the Examiner has not shown that Cullen *et al.* discloses all of the features of independent claim 1. Since the cited reference has not been shown to anticipate

claim 1, neither does it anticipate dependent claims 2-16. As such, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(e).

VII. Claim Rejections under 35 U.S.C. § 103

A. Rejection of Claims 1-13 and 16

Claims 1-13 and 16 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Tanihara *et al.* (U.S. Patent No. 5,658,592) in view of Wren (U.S. Patent No. 5,238,685) in further view of Plendl *et al.* (Biol. Chem., 2000, 381: 11-3-1115) in further view of Ulbrich *et al.* (Biomaterials, 1982, 3: 150-154 and Biomaterials, 198, 1: 199-204) and in further view of Chagas *et al.* (Biochem. J., 1995, 306: 63-69). *Office Action* at page 12. Applicants respectfully traverse for at least the following reasons.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of skill in the art, to modify the reference or to combine reference teachings. Moreover, there must be a reasonable expectation of success. A teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). "If the proposed combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." MPEP § 2143.02 IV (citing *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)).

Amended claim 1 is directed to a wound dressing comprising a therapeutic agent and a matrix comprising polymers joined by cross-linkages which cross-linkages comprise oligopeptidic sequences which are cleavable by a kallikrein such that the rate of release of the therapeutic agent increases in the presence of the kallikrein, where the oligopeptidic sequence comprises of -Phe-Arg-Ser-Ser-Arg-Gln- or Met-Ile-Ser-Leu-Met-Lys-Arg-Pro-Gln-.

The Examiner acknowledges that Tanihara *et al.* and Wren "do not teach the oligopeptidic sequences Phe-Arg-Ser-Ser-Arg-Gln or Met-Ile-Ser-Leu-Met-Lys-Arg-Pro-Gln, Kallikrein and the HPMA as the polymer." *Office Action* at page 14. Instead, the Examiner relies on Plendl *et al.*, Ulbrich *et al.*, and Chagas *et al.* to rectify the acknowledged deficiencies of Tanihara *et al.* and Wren.

Assuming, *arguendo*, that one were motivated to combine the references as suggested by the Examiner, the skilled artisan would still not obtain the currently claimed invention.

The Examiner states that "it would be obvious to substitute the linker 'C' group of Tanihara's teaching with a peptide linker, because kallikreins are found at wound sites and they cleave at Arg-Ser and Met-Lys bonds," and that it "would be further obvious to substitute HPMA for the polymer gel drug delivery system in Tanihara, because biodegradable polymers, such as HPMA could be used in drug delivery system, as taught by Ulbrich et al (1982)." *Office Action* at page 16. However, as described below, even combining all of the six references as suggested by the Examiner would result in a drug being immobilized (*i.e.* joined) to an HPMA polymer via an oligopeptidic sequence. This is in contrast to the currently claimed wound dressing where the polymers are joined by cross-linkages comprising oligopeptidic sequences.

The primary reference relied on by the Examiner, Tanihara *et al.*, discloses a medical polymer produced "by immobilizing a drug, through a cleavable group with the main chain to be cleaved via an enzymatic reaction and a spacer, onto a water swelling polymer gel." Tanihara *et al. Column 7, lines 6-10.* As the Examiner apparently recognizes, the drug is bound to the cleavable group in noting that Tanihara *et al.* "teaches that when a cleavable group ... and a drug are bound together via an ester bonding...." *Office Action* at page 13. Indeed, Tanihara *et al.* teach that such drugs must be immobilized by a cleavable group to the polymer gel to achieve the objective of the invention disclosed in Tanihara. Tanihara *et al.* teach that one of the problems associated with prior medical polymers used in drug delivery was that known polymers were not able to release a therapeutically effective amount of a drug at a subjective focal site. Tanihara *et al. Column 5, lines 15-17.* The inventors go on to note that their first objective was to "provide a medical polymer gel capable of releasing a therapeutically effective dose of a drug only at a focal site generating an enzyme," and that such objective was achieved by immobilizing a drug "onto a water swelling polymer gel through a cleavable group...." *Id.* at lines 19-38. Tanihara *et al.* specifically discloses, the invention "is characterized in that a drug is immobilized, through a cleavable group with the main chain to be cleaved with an enzymatic reaction and a spacer, onto a water swelling polymer gel, wherein the drug is bound in the form represented by the general formula (I) [A-B-C-D]." Tanihara *et al., at Column 12, lines 15-19* (emphasis added).

In contrast, the present disclosure provides for delivery of therapeutic agent to a site by increasing pore sizes in the matrix by the enzymatic action of kallikreins. The therapeutic agent is contained within or beside a matrix of polymers crosslinked to each other by oligopeptide sequences. As the present specification discusses, "[t]he principle underlying

the present invention is that the cross-linked polymers would behave as both an enzyme sensor and as an [sic] pain-dependent delivery system." Specification at page 3, lines 27-29. The specification discloses that in "the absence of elevated levels of kallikreins the oligopeptidic sequences remain intact, keeping pore size small and preventing (or at least keeping to low levels) the release of the therapeutic agent. Elevated pain protease (e.g. in wound infection or wound chronicity) hydrolyse the oligopeptidic sequences which results in increased pore size and permeability." *Id.* at lines 29-33.

Moreover, Tanihara *et al.* teaches away from making the modifications suggested by the Examiner. Tanihara suggests that the problems of the art were overcome by immobilizing a drug onto a polymer, and that satisfactory drug delivery could not be achieved without immobilizing the drug using the spacer element "B" and a cleavable group "C." For example, Tanihara *et al.* discloses that "if a drug is immobilized using only a cleavable group with the main chain to be cleaved with an enzymatic reaction, the cleavage reaction of the cleavable group with the enzyme is very slow, so that a therapeutically effective amount of the drug cannot be released." Tanihara *et al. Column 12, lines 23-27.* In addition, the reference suggests that if "only the spacer is used, the drug is not successfully released at a site where the enzyme is present." *Id.* at lines 27-29. Accordingly, Tanihara *et al.* suggest that to achieve the objectives of Tanihara, the drug is to be immobilized onto a polymer using both the spacer and the cleavable groups.

The Examiner has provided no support that the disclosures of Tanihara *et al.*, Wren, Plendl *et al.* Ulbrich *et al.* or Chagas *et al.* would have led one of ordinary skill in the art to combine or modify the teachings therein to obtain the subject matter defined in the rejected claims. According to the Office Action, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to modify the linker "C" group of Tanihara *et al.* and include components of Wren, Plendl, Ulbrich, and Chagas to arrive at the currently claimed invention. However, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P. § 2143.01 (citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)) (emphasis original). Indeed, as noted by the Examiner, " Tanihara teaches that Wren is deficient because "the drugs are consistently released because the drugs are not immobilized onto the gel." *Office Action* at pages 12-13. Accordingly, the Examiner has provided no support or explanation for the assertion that the skilled artisan would have been motivated to combine the references in view of the express teaching in the

primary reference, Tanihara, of the deficiencies of Wren, or that any of the cited references suggests such a combination.

The Examiner has pointed to nothing in any of the cited references that would have led one of ordinary skill in the art to combine or modify the teachings therein to obtain the subject matter defined in the rejected claims. In view of the foregoing, a *prima facie* case has not been made. There is no motivation to combine and/or modify Tanihara *et al.* in the manner alleged, and even if the combinations were made, the result would not be a wound dressing as currently claimed. Thus, Applicants respectfully request that the rejections of claims 1- 13 and 16 under 35 U.S.C. § 103(a) be withdrawn.

B. Rejection of Claims 14 and 15

Dependent claims 14 and 15 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Tanihara *et al.* (U.S. Patent No. 5,658,592) as applied to claims 1-13 and 16, and further in view of Rawlings *et al.* (U.S. Patent No. 5,010,883). Applicants respectfully traverse for at least the following reasons.

Independent claim 1 and Tanihara *et al.* are discussed above. As noted, the Examiner has not established that the teachings of Tanihara *et al.*, alone or in combination with multiple additional cited references, discloses all of the features of the currently claimed invention. Dependent claims 14 and 15 involve a wound dressing having an absorbent layer provided behind a barrier layer and the therapeutic substance is dispersed in the absorbent layer, where the barrier layer may substantially encapsulate the therapeutic agent. Again, the present specification discusses that, "[t]he principle underlying the present invention is that the cross-linked polymers would behave as both an enzyme sensor and as an [sic] pain-dependent delivery system." Specification at page 3, lines 27-29. The specification discloses that in "the absence of elevated levels of kallikreins the oligopeptidic sequences remain intact, keeping pore size small and preventing (or at least keeping to low levels) the release of the therapeutic agent. Elevated pain protease (e.g. in wound infection or wound chronicity) hydrolyse the oligopeptidic sequences which results in increased pore size and permeability." *Id.* at lines 29-33. Nor has the Examiner argued that Rawlings *et al.* disclose such a feature.

In view of the foregoing, a *prima facie* case has not been made. There is no motivation to combine and/or modify Tanihara *et al.* in the manner alleged, and even if the combinations were made, the result would not be a wound dressing as claimed. Thus,

Applicants respectfully request that the rejections of claims 14 and 15 under 35 U.S.C. § 103(a) be withdrawn.

VIII. Claim Rejections – Nonstatutory Double Patenting

Claims 1-16 are provisionally rejected for nonstatutory obviousness-type double patenting over claim 1 of commonly assigned copending Application No. 10/497,442. This rejection is obviated by amendment to the claims. In particular, none of the currently claimed wound dressings comprising, for example, matrices having polymers joined by cross-linkages comprising the recited oligopeptidic sequences are recited in the cited application. Moreover, the Examiner has not shown that it would have been obvious to form such matrices based on the '442 Application. Accordingly, it respectfully requested that the Examiner withdraw this rejection.

For the foregoing reasons, claims 1-4 and 7-17 are considered allowable. A Notice to this effect is respectfully requested. If any questions remain, the Examiner is invited to contact the undersigned at the number given below.

Respectfully submitted,

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Date of Signing: April 5, 2007